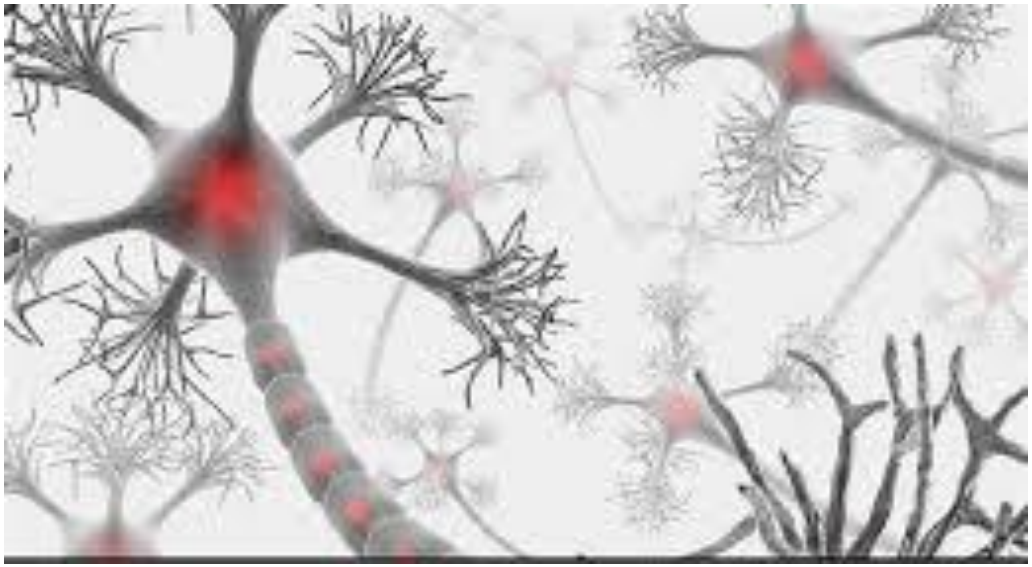
Synthesis,Storage,Release and Functions of different Neurotransmitters



By

Dr SAIMA SHAHEEN

Learning objectives

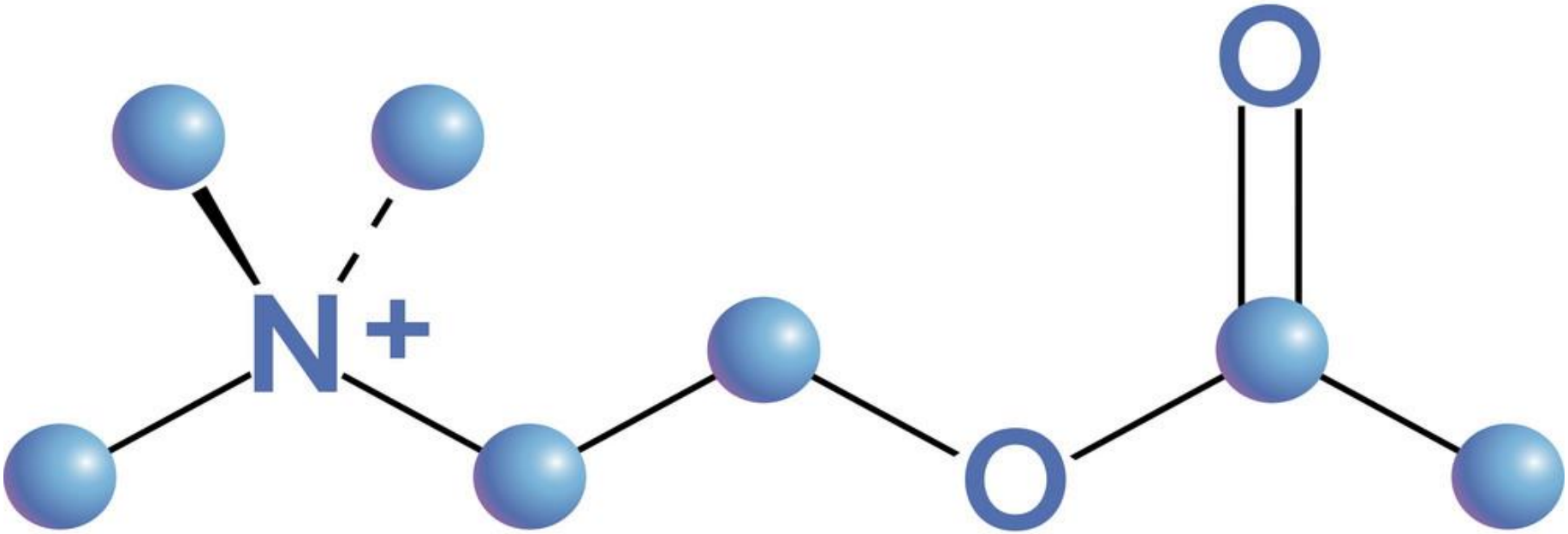
Synthesis, storage ,release and actions of

- Acetylcholine
- Catecholamine
- Serotonin
- Histamine
- GABA
- Glycine & Glutamate
- Nitrous oxide

Classification of neurotransmitters

- Depending upon chemical nature

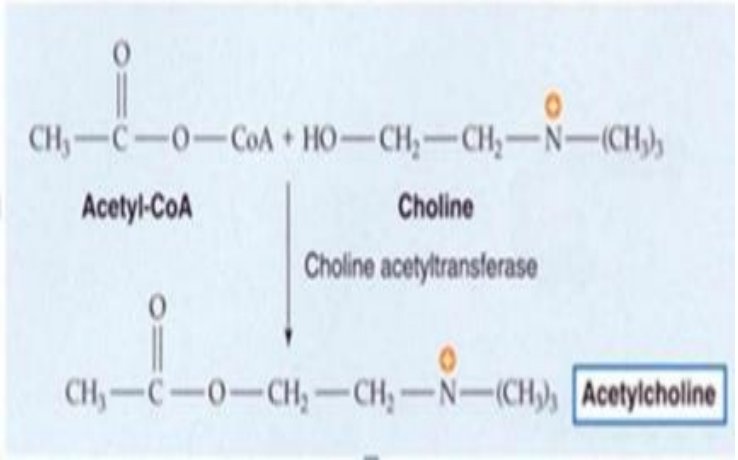
CLASS	EXAMPLE	DERIVED FROM
AMINES	Epinephrine, Norepinephrine Dopamine	Tyrosine
	Serotonin	Tryptophan
	Histamine	Histidine
AMINO ACID AND AMINO ACID DERIVATIVES	Glutamate	
	Aspartate	
	Glycine	
	GABA	Glutamate
PURINES	Adenosine	ATP
	ATP	
GAS	Nitric oxide	Arginine
Miscellaneous	Acetylcholine	Choline



Acetylcholine

Acetylcholine (Ach)

- Acetylcholine was first neurotransmitter to be discovered.
- Isolated by German biologist named Otto Loewi.
- It is a neurotransmitter between axon and striated muscles at neuromuscular junction.
- Neurons that synthesize and release it are termed cholinergic neurons.



Synthesis and storage

- Synthesized in neuronal cytoplasm.
- For synthesis we require two things

1)Acetyl-CoA which comes from
pyruvate metabolism

2)(Choline is obtained from

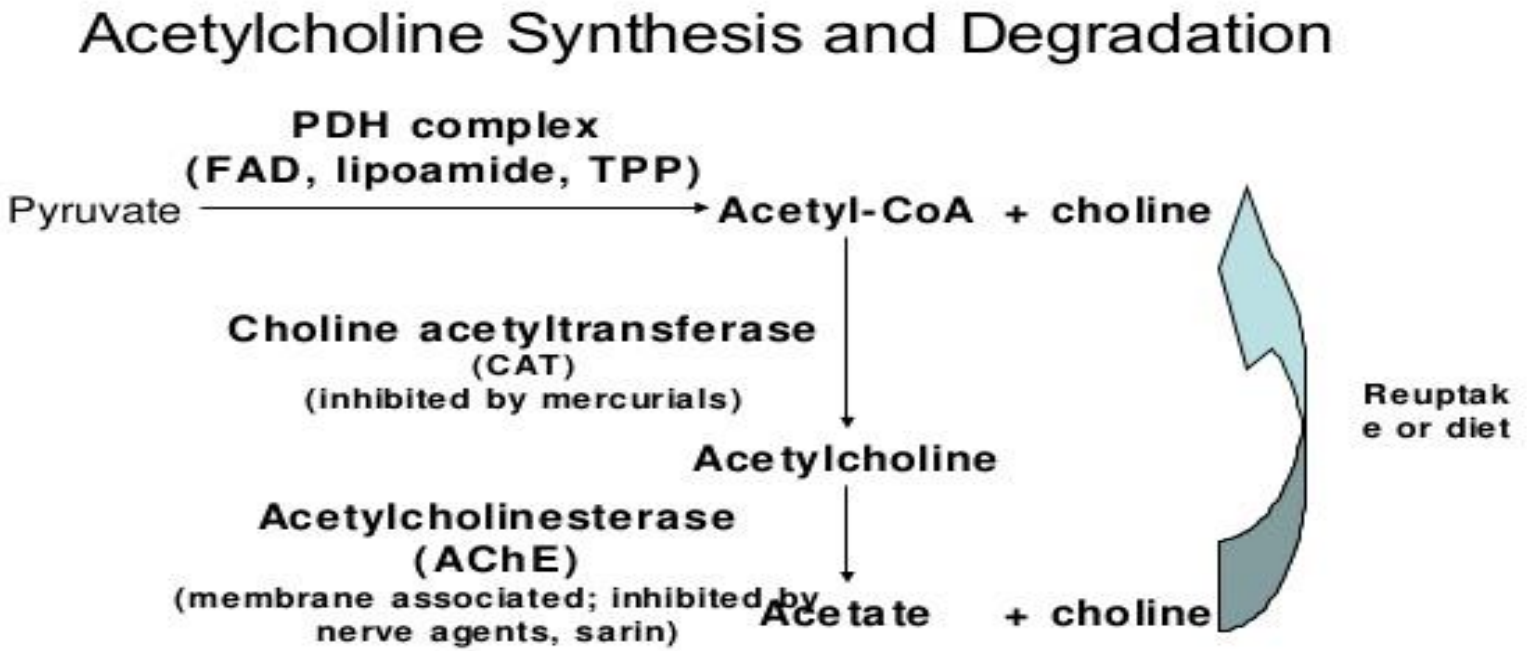
1)Exogenous
food(folic acid ,B_{12})

2)Endogenous
biosynthesis from Glycine or reuptaken after degradation.

storage

1)Incorporated in synaptic vesicles and stored therein.

Synthesis and storage



Release ,Reuptake and degradation

1)Release is Ca^{+2} dependent.

2)Degraded by specific enzyme

1) Acetyl cholinesterase present in synaptic space.

2)Non specific esterases pseudocholine esterases found in tissues and plasma.

Reuptake:

By specific choline transporters

Functions of acetylcholine

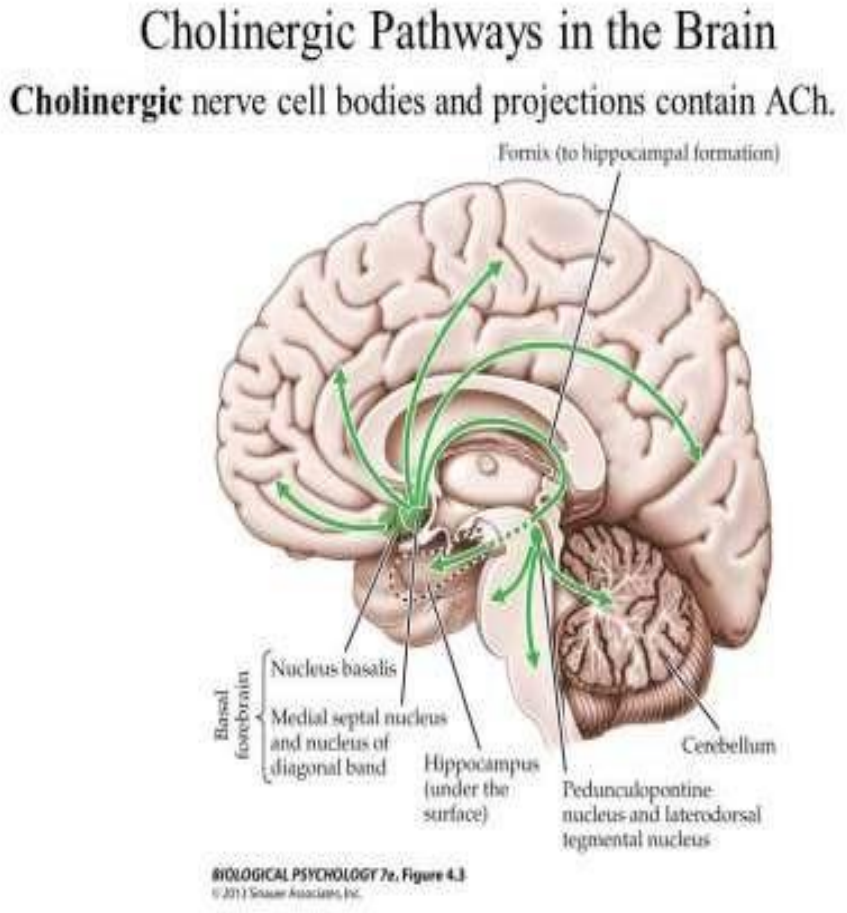
- Function in both peripheral and central nervous system.
- In peripheral nervous system it contracts skeletal muscles.
- In CNS it plays role in

  signal of muscle movement, sensation of pain,

  learning& memory formation, regulation of endocrine system,

  rapid eye movement sleep cycle.

Acetylcholine

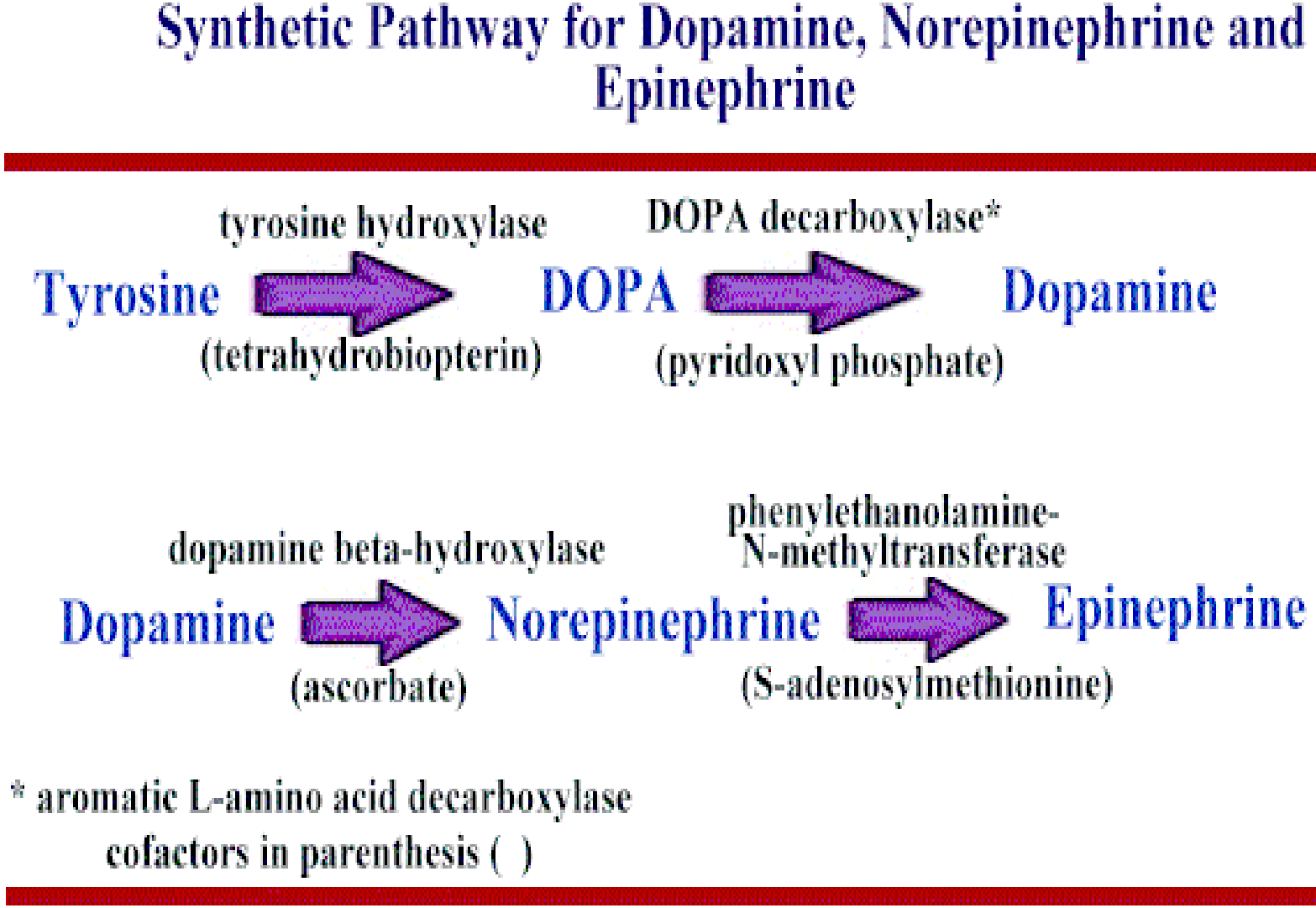


- The degeneration of particular cholinergic pathways is a hallmark of Alzheimer disease.

Catecholamines

www.emmasaying.com

Synthesis of catecholamines



STORAGE AND RELEASE

- STORED IN CHROMAFFIN GRANULES OF ADRENAL GLAND.
- RELEASE IS Ca dependent.

Monoamines

- **Dopamine (DA):**
  - DA is the precursor of norepinephrine and it is the Predominant catecholamine in the CNS.
  - DA play a role in motivation and reward (most drugs of abuse increase DA signaling), motor control, and the release of various hormones.

Dopamine Receptor

Dopamine Receptor	Function
D1	Regulates neuronal growth & development, voluntary movement, feeding behavior, affect, reward, sleep, attention, impulse control memory, renal receptors help control renin secretion
D2	Memory, regulation of locomotion, regulation of renal function, blood pressure, vasodilation, GI motility
D3	Cognitive, emotional, and endocrine functions, regulation of locomotor effects
D4	Regulation of renal function, blood pressure, vasodilation, GI motility
D5	Neuroendocrine functions

- . DA-containing pathways and receptors have been implicated in the pathophysiology of schizophrenia and Parkinson disease and in the side effects seen following pharmacotherapy of these disorder.
- Causes may be:
- the drop in the amount of dopamine made by the body
- or a problem with receptors in the brain,
- or damage to the nerves in the brain.

- **Norepinephrine (NE):**
  - Large amounts of NE present within the hypothalamus and in certain zones of the limbic system (e.g., the central nucleus of the amygdala, the dentate gyrus of the hippocampus).
  - NE also is present in lower amounts in most brain regions.
  - NE is an endogenous neurotransmitter for the α and β adrenergic receptor subtypes that are present in the CNS.

Central Neurotransmitters - Monoamines

- **Epinephrine (EPI):**
  - NE is converted into EPI by enzyme phenylethanolamine-N-methyltransferase.
  - EPI-containing neurons are found in the medullary reticular formation and diencephalic nuclei.

Receptors of Norepinephrine & Epinephrine

Receptor	Major Effector Tissues	Major Functions
$Alpha_1$	SM, sphincters	Contraction (constriction),
$Alpha_2$	Nerve endings	↓ Transmitter release
$Beta_1$	Cardiac muscle, Kidney	↑Heart rate and force, ↑Renin secretion
$Beta_2$	SM including bronchi Liver Skeletal muscle	Relax SM ↑ Gluconeogenesis, glycogenolysis ↑ Glycogenolysis and K+ uptake
$Beta_3$	Adipose	↑ Lipolysis
DA_1	SM especially renal, mesenteric and cardiac	Relax renal vascular SM (higher doses activates $\beta 1$ and $\alpha 1$ receptors)

Functions of catecholamine

- Inhibitory and excitatory effects on peripheral nervous system.
- Excitatory effect exerted upon
- Smooth muscles of vessels
- Heart ,which lead to an increase in heart rate and force of contraction.
- Inhibitory effects exerted upon
- Smooth muscle cells in the wall of gut, bronchial tree of lungs and vessels that supply blood to skeletal muscle.

Functions of catecholamines

***Nor epinephrine and epinephrine influence the rate of metabolism by modulating

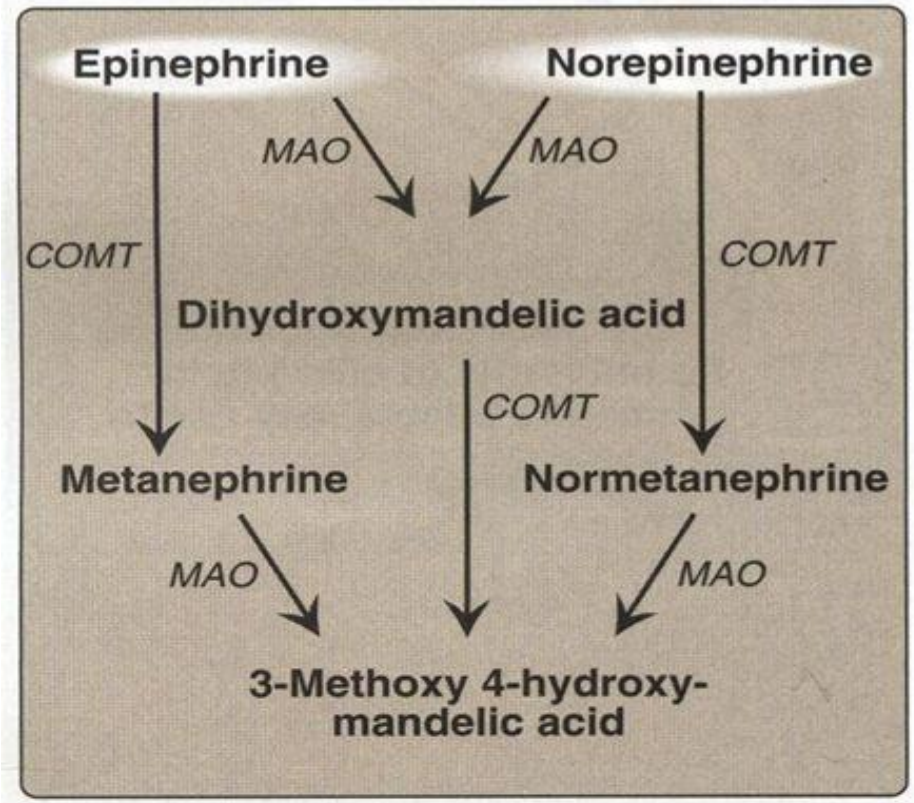
- Endocrine function such as

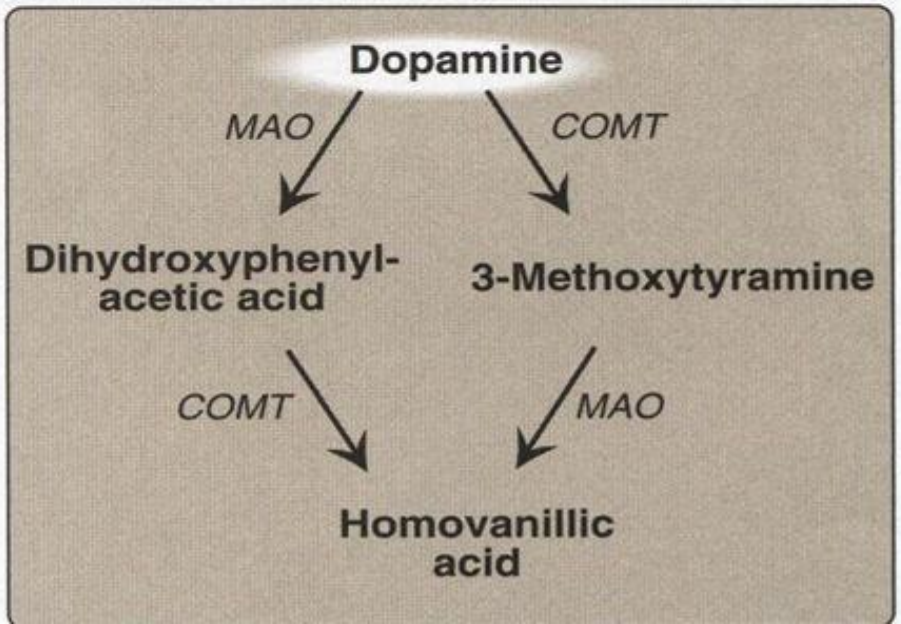
1) insulin secretion and

2) by increasing the rate of glycogenolysis and fatty acid mobilization.

Degradation of catecholamines

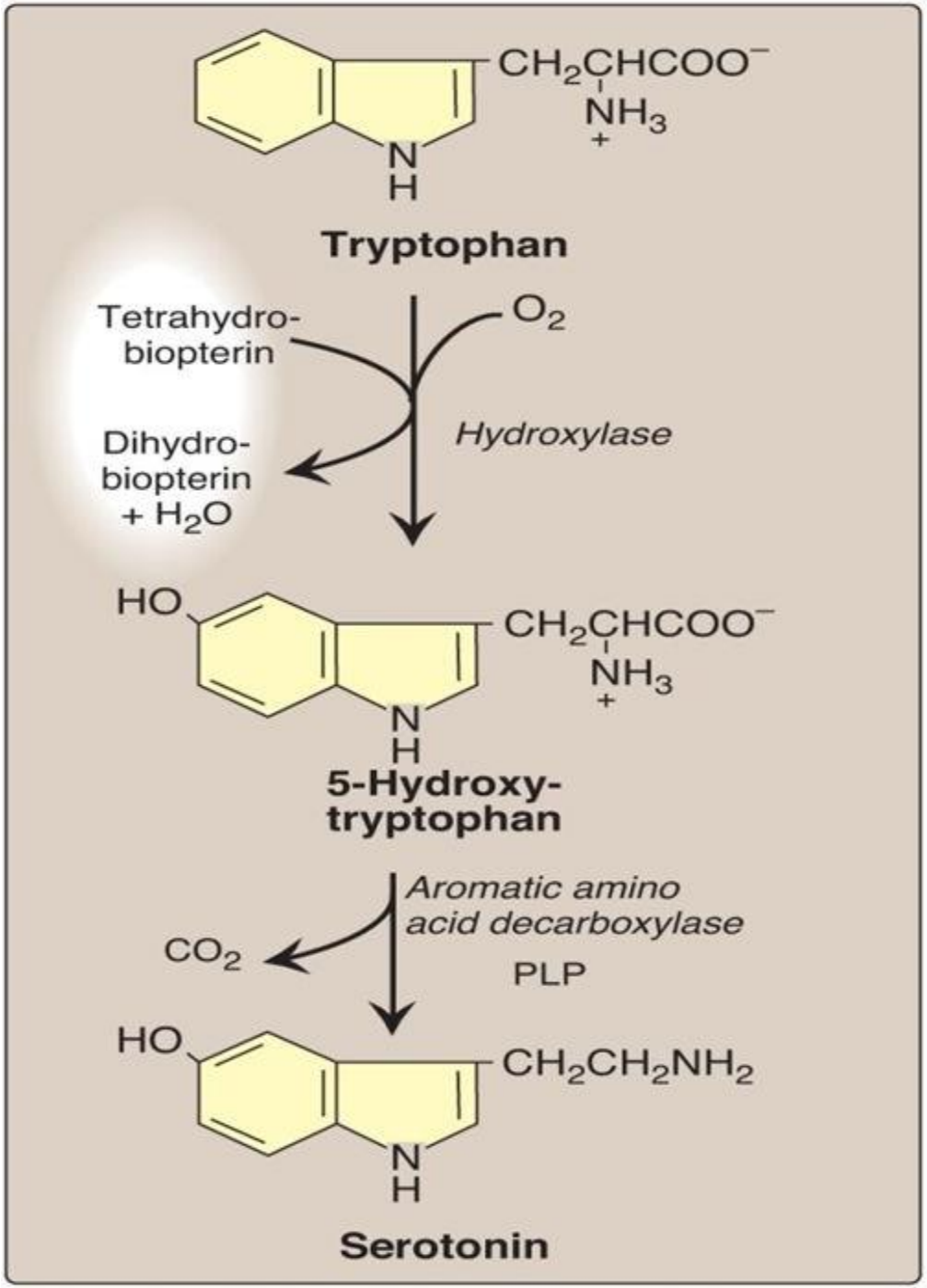
- Reuptake by high affinity mechanism.
- Deaminated by monoamin oxidase to dihydroxymandelic acid
- Released as such or is methylated by catechol-o-methyltransferase to form 3-methoxy-4-hydroxymandelic acid within the nerve terminal and then excreted.





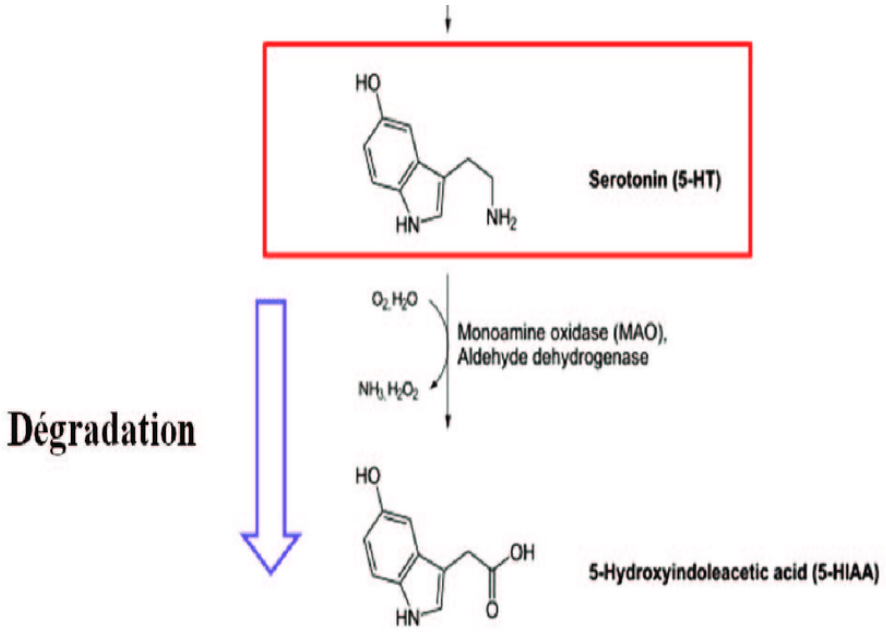
serotonin

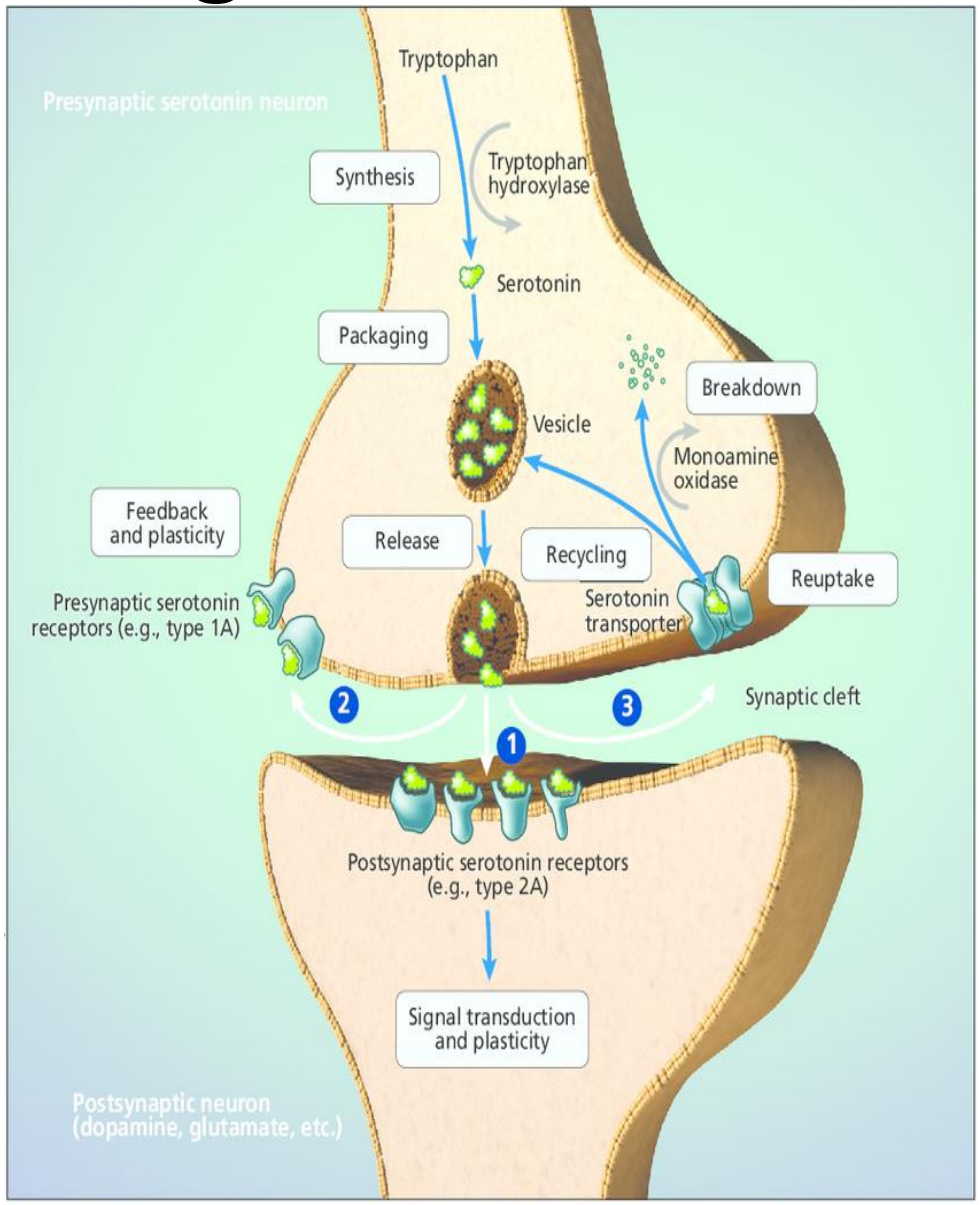
- Synthesis occur within neural tissue(serotonergic neurons) and in elementary epithelium.
- Found in
- Entero chromaffin cells of GIT(90%).
- Platelets and CNS
- Stored in
- vesicles in axon terminals.



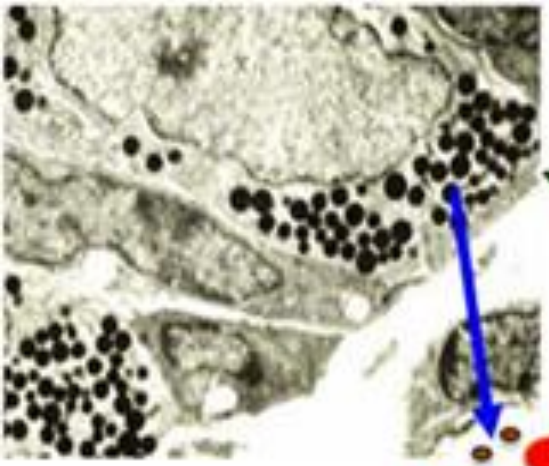
Reuptake and degradation

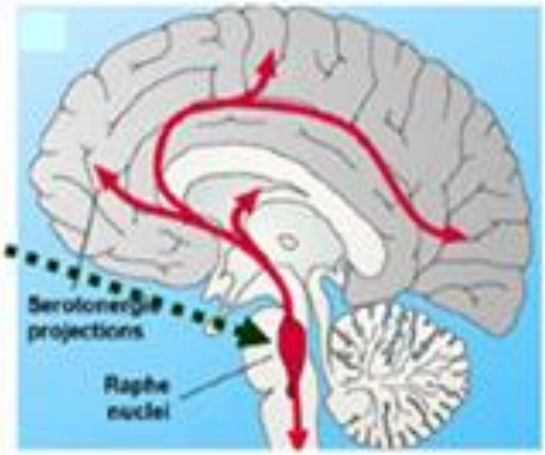
- Taken up by Na^+ dependent high affinity process





Functions of serotonin





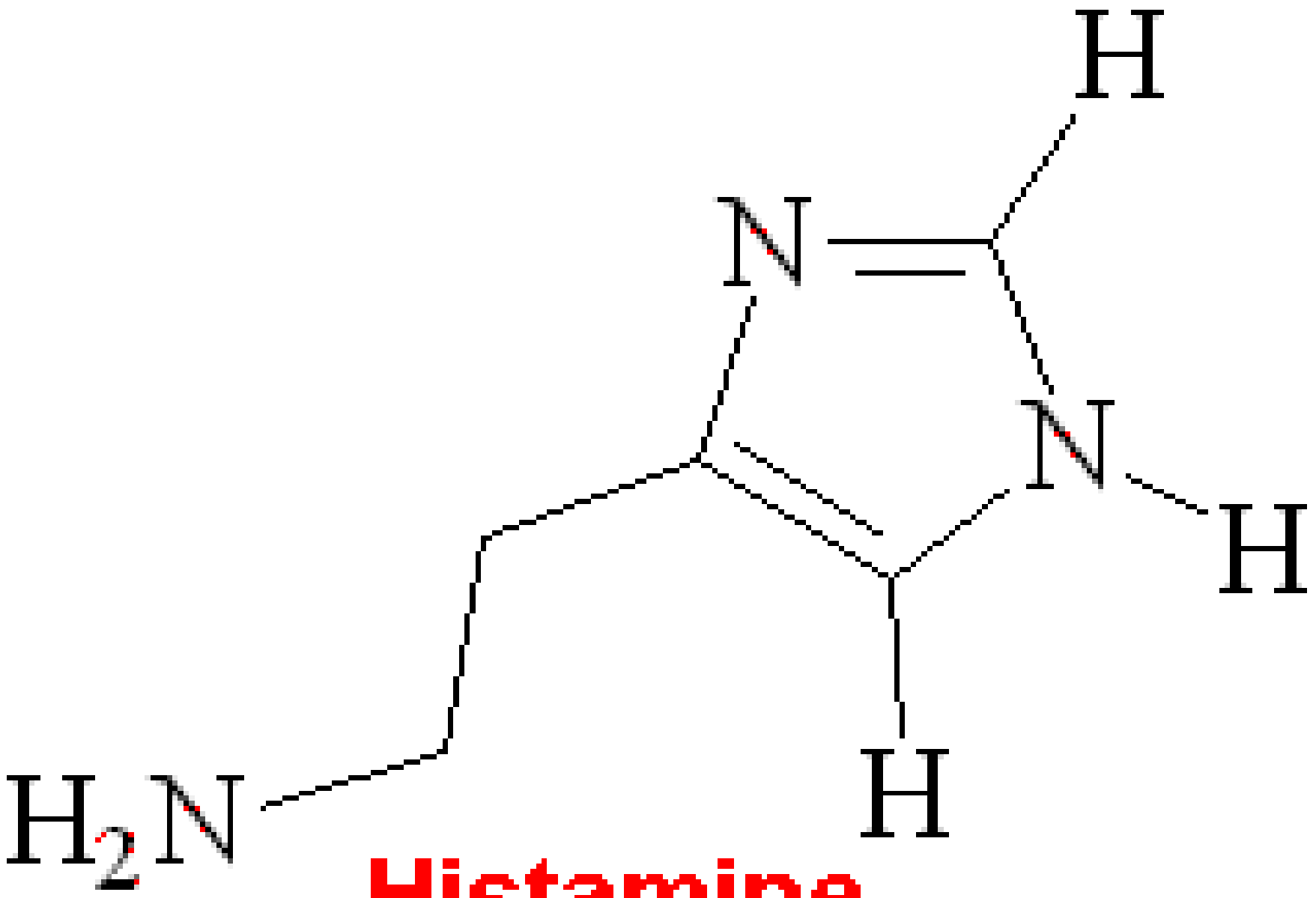
Tryptophan

TPH1 → Serotonin

TPH2 → Serotonin

Peripheral effects:
- vascular tone
- hemostasis
- cell regeneration
- heart functions
- organ development
- intestinal motility
- immuno-modulation
- others

Central effects:
- depression
- sleep
- aggression
- food intake
- psychosis
- anxiety
- others



Histamine

*Biogenic amine

* Synthesized from

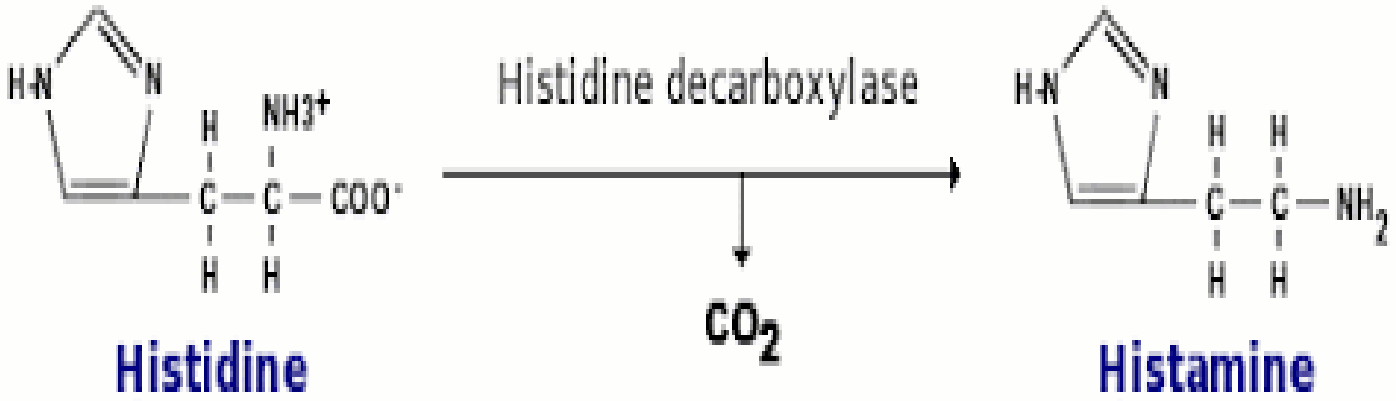
*Histidine

Found in

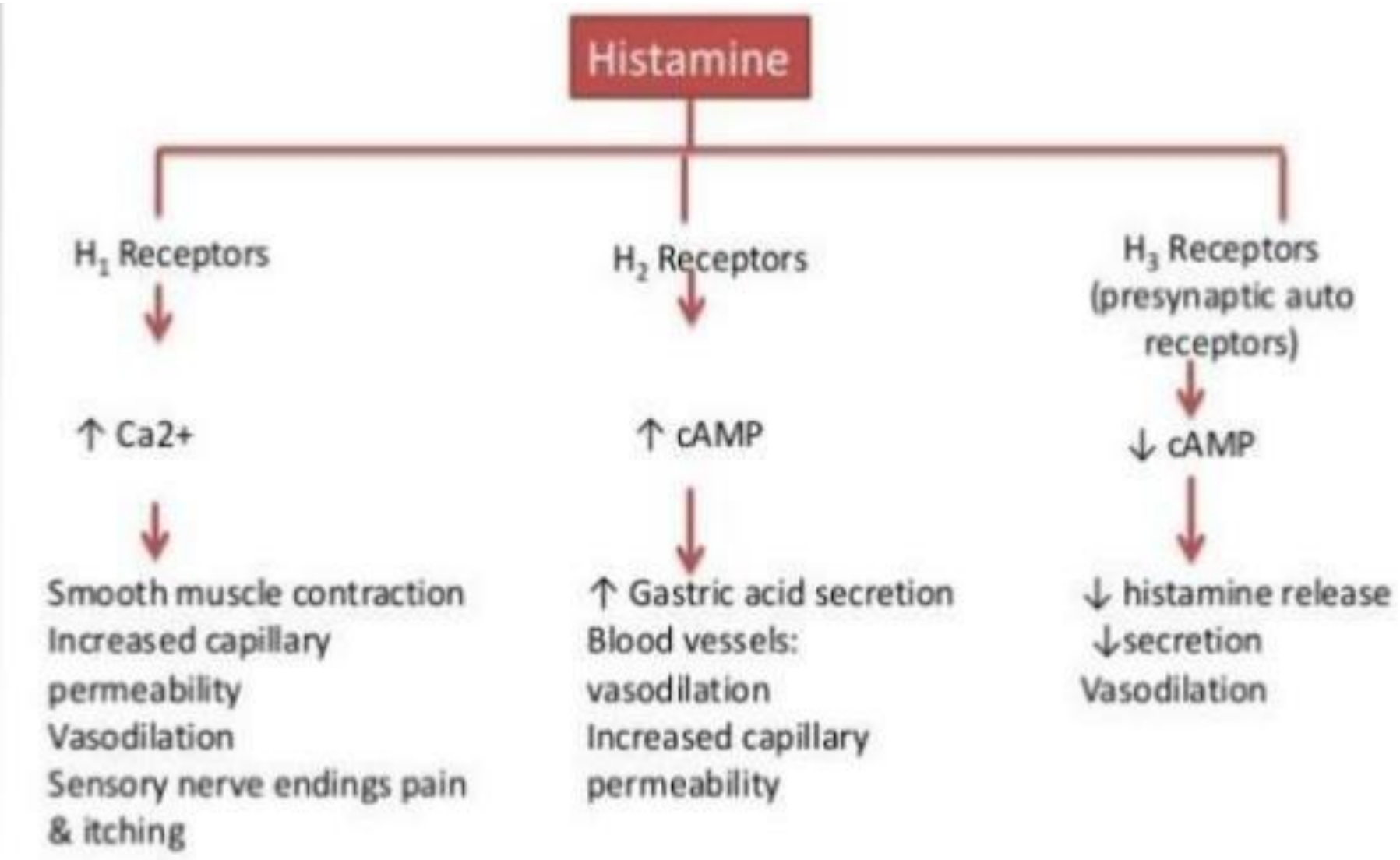
1) hypothalamus,

2)High amount in lung,skin and GIT.

3)High conc in mast cells or basophils



Mechanism of action of histamine

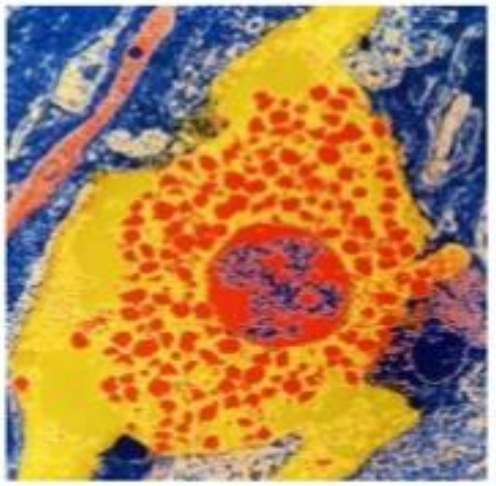


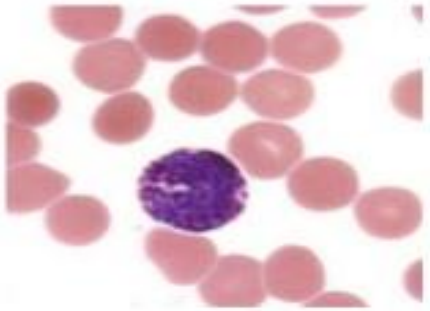
STORAGE

Storage of histamine

- **Mast cells**
- **Basophils**
- **Histaminocytes (stomach)**
- **Histaminergic neurons**

✓Stored in secretory granules
✓high in skin, bronchial mucosa and intestinal mucosa

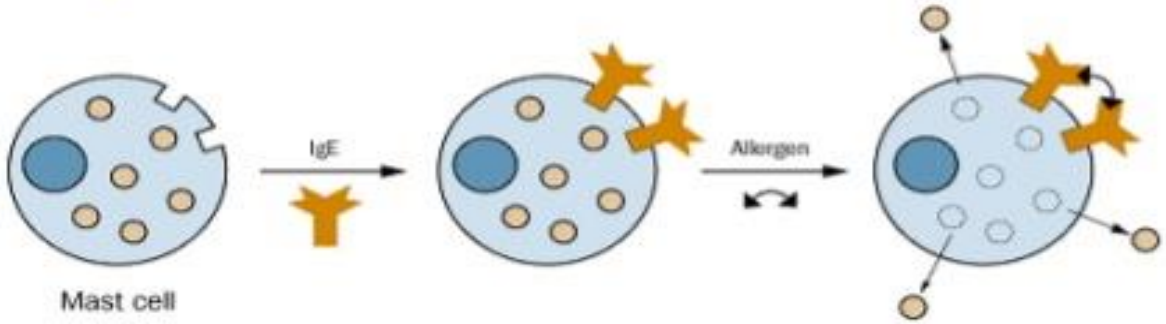




HOW IS HISTAMINE RELEASED

Release of histamine

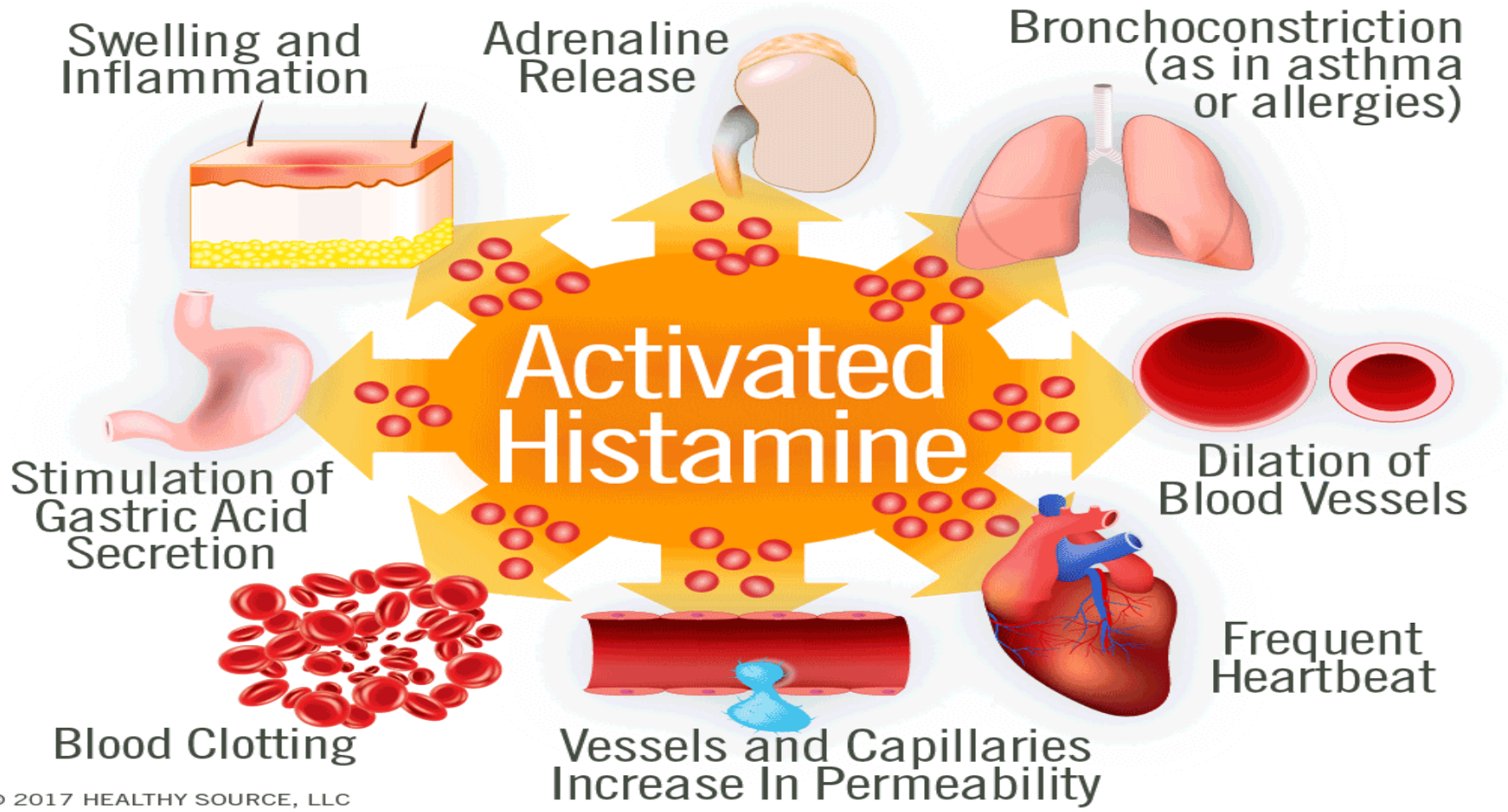
- **Immunologic release**



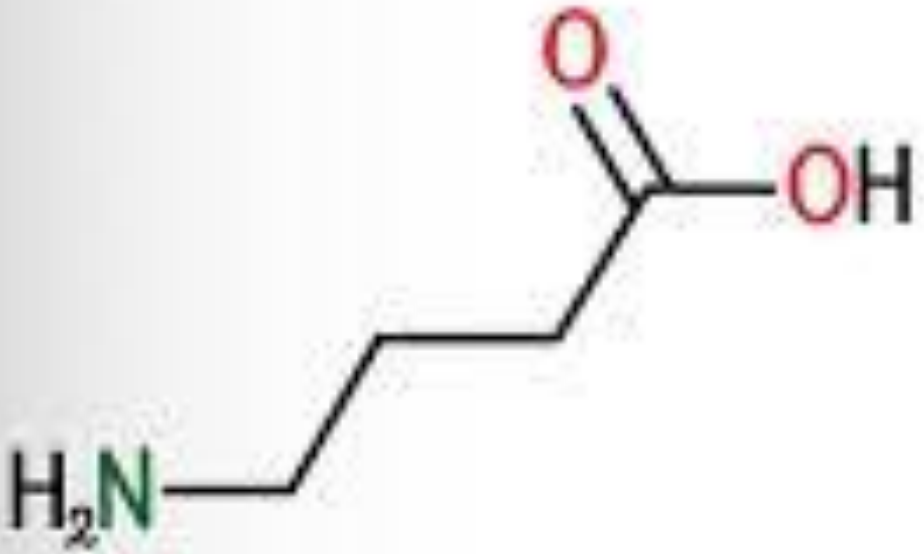
Exposure of an antigen to a previously sensitized (exposed) subject can immediately trigger allergic reactions. If sensitized by IgE antibodies attached to their surface membranes will degranulate when exposed to the appropriate antigen and release histamine, ATP and other mediators

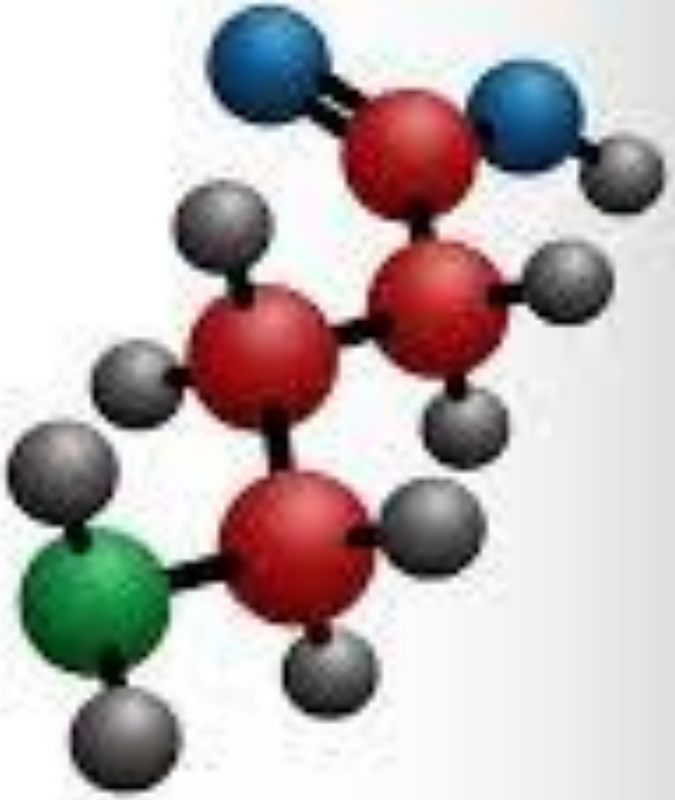
- **Chemical & mechanical release due to mast cell injury**

FUNCTIONS OF HISTAMINE



gamma-Aminobutyric acid

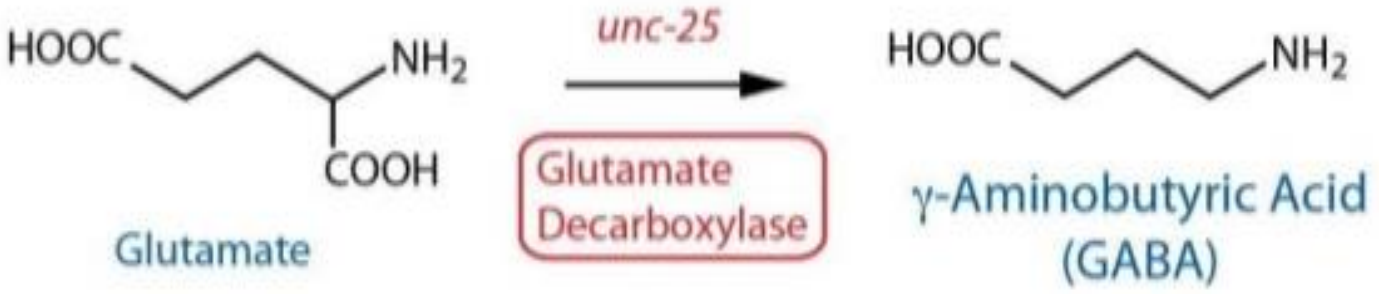




$C_4H_9NO_2$

Gamma amino butyric acid

- GABA is the main inhibitory neurotransmitter in the CNS.
- Synthesized in the brain from Glutamate decarboxylase(GAD) in many nerve endings of the brain and β-cells of pancreas.GAD acts as catalyst that remove carboxyl group from glutamate.



STORAGE AND RELEASE

STORAGE

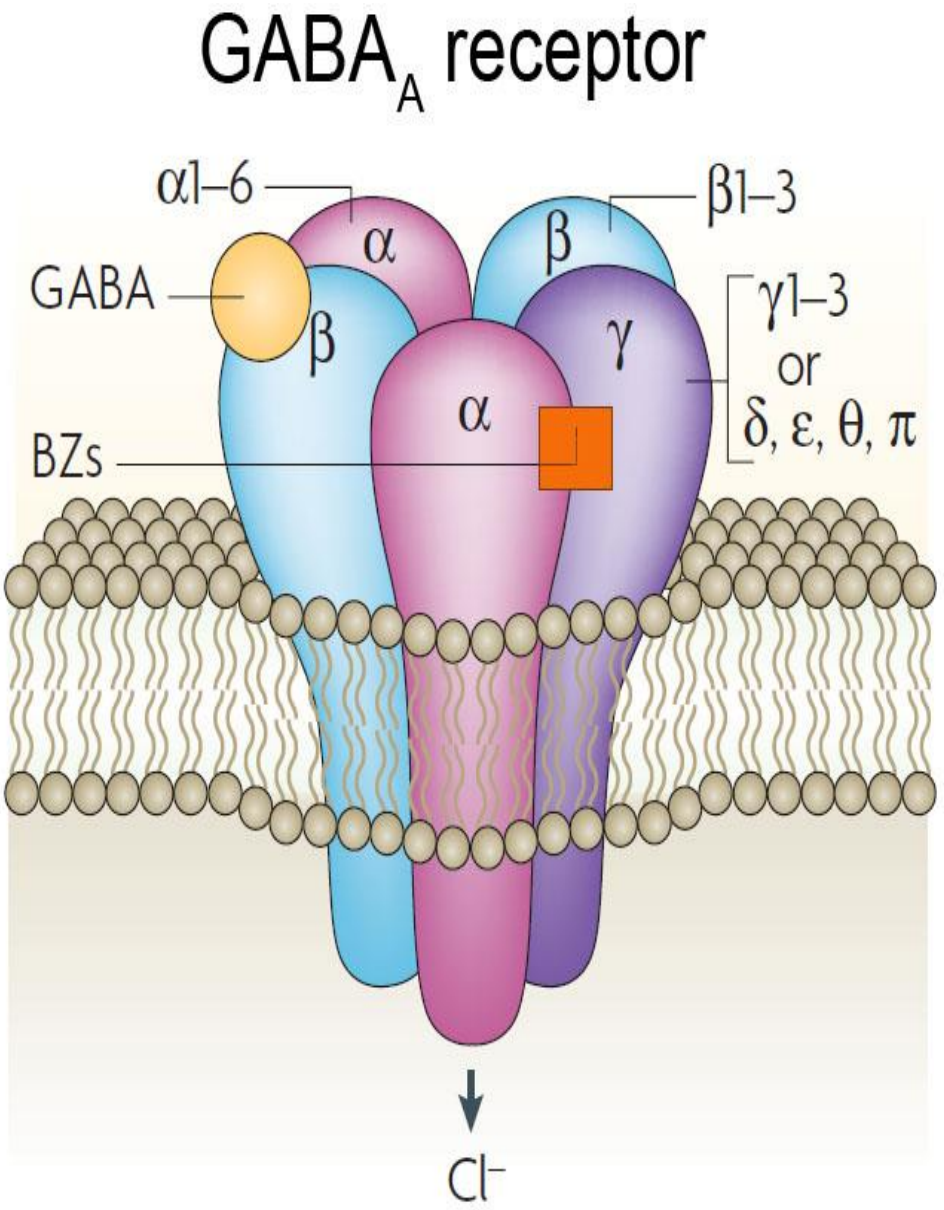
- Newly synthesized GABA is stored in synaptic vesicle by means of vesicular transporter.
- These are stored at postsynaptic terminal untill action potential release.

RELEASE

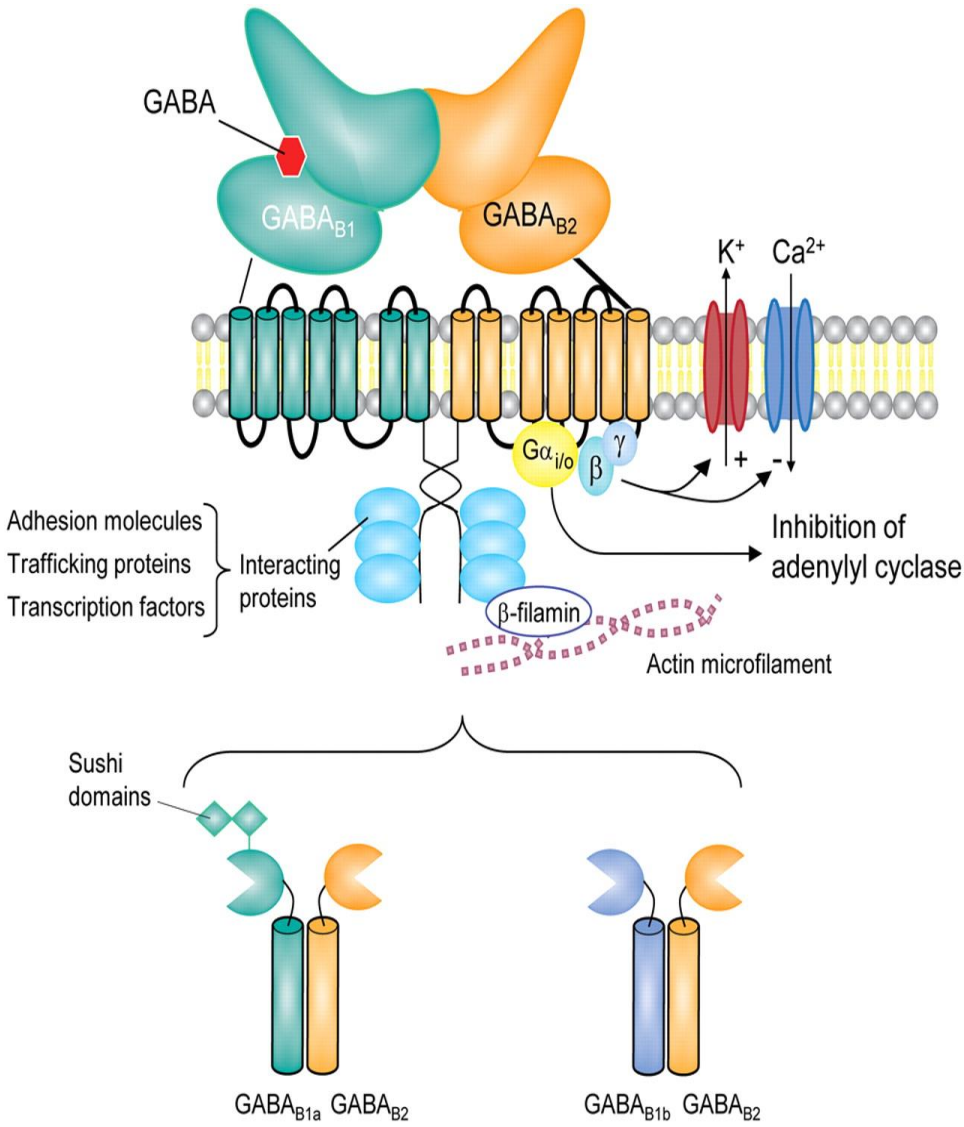
- Stored GABA releases into synaptic cleft stimulated by depolarisation of presynaptic neurons.
- GABA diffuses across the cleft to target receptors on postsynaptic surface.
- The action of GABA is terminated by reuptake of GABA by presynaptic nerve terminals & glial cells

Receptors and actions

- Two types of receptors
- GABA-A receptors
- Pentameric structure
- Functions as Cl^- channel
- Increase conductance of Cl^- from outside causing hyper polarization and decrease nerve excitability.



- GABA-B receptors
- Hetero dimer
- b1&b2 subunits
- B1 subunit has GABA binding site
- B2 linked with G-protein
- Decrease Ca^{2+} conductance
- Increase k^{+} conductance.
- GABA-B receptors lack diazepam & barbiturate binding sites.



Functions of GABA

- Relieves anxiety.
- Relieve pain.
- Regulate release of growth hormone & sex hormones.
- Prevent formation of fat.
- Treating attention deficit hyperactivity syndrome
- Stabilize blood pressure
- Decrease blood sugar level in diabetes


Top 3 Gaba Deficiency Symptoms
1. Anxiety and Depression
2. General Uneasy Feeling
3. Can't Sit Still For Long Periods of Time

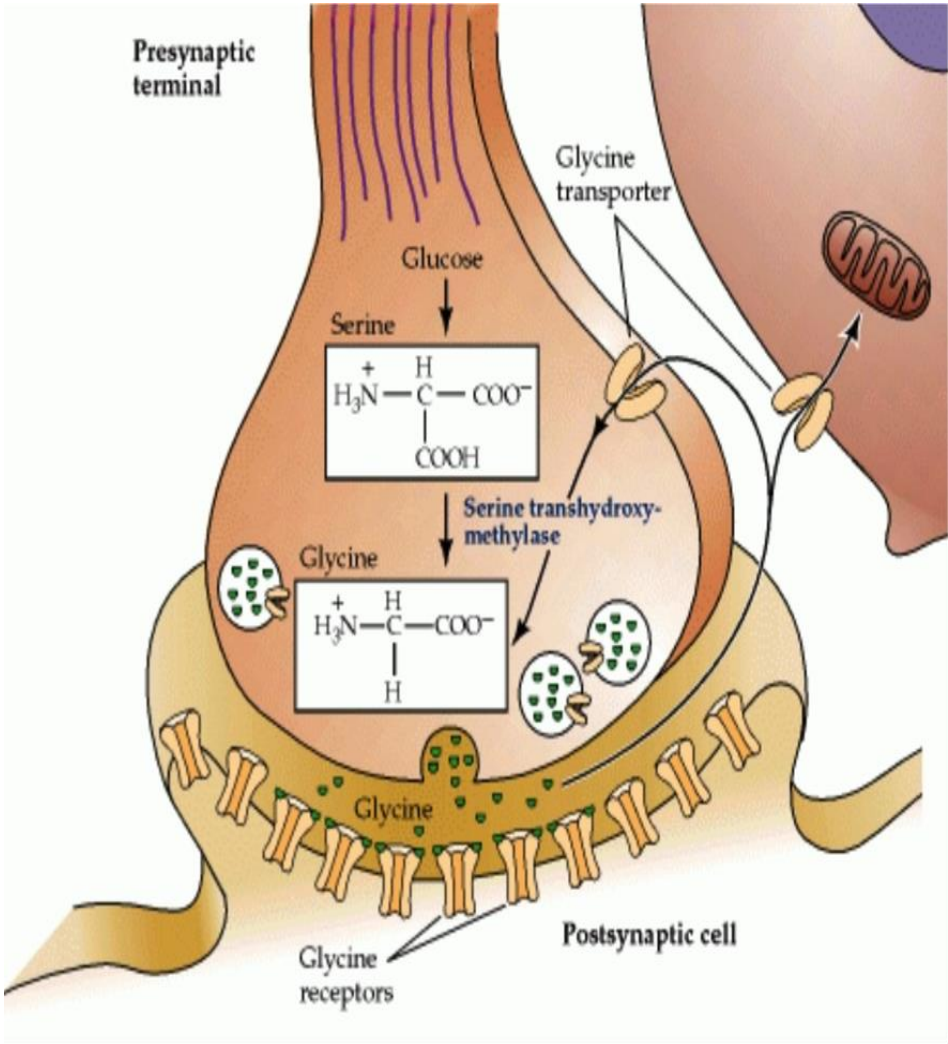

Glycine
O
H2N OH

GLYCINE

- Glycine is a semi-essential amino acid.
- Major inhibitory neurotransmitter in the spinal cord.
- Glycinergic receptors are abundant in spinal cord and brain stem.
- Also in higher brain regions including the hippocampus.

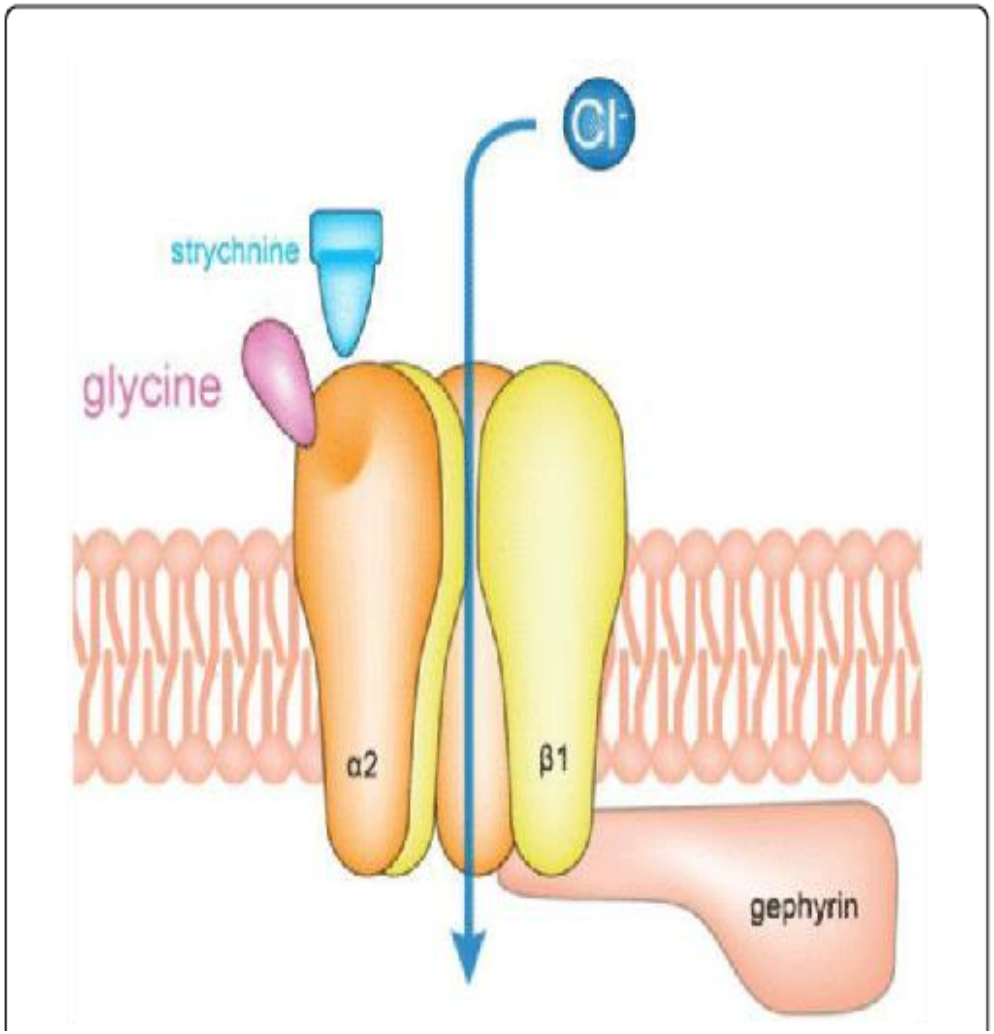
Synthesis , storage & release

- Synthesized from serine. By serine hydroxy methyltransferase.
- Stored in secretary vesicles.
- Released by Ca^{2+} dependent exocytosis.



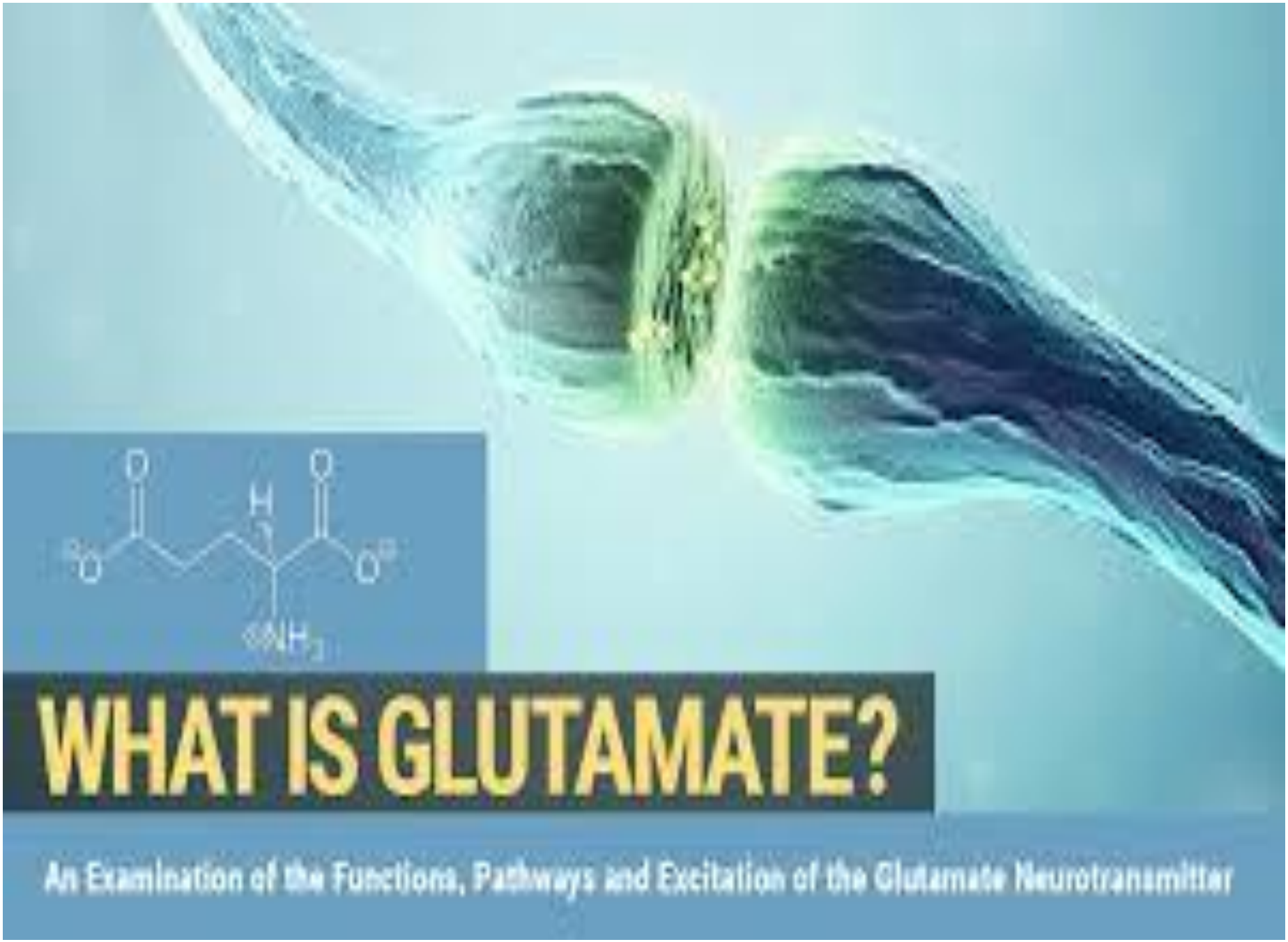
Receptors

- Increase Cl^- influx
- Hyperpolarize postsynaptic membrane.



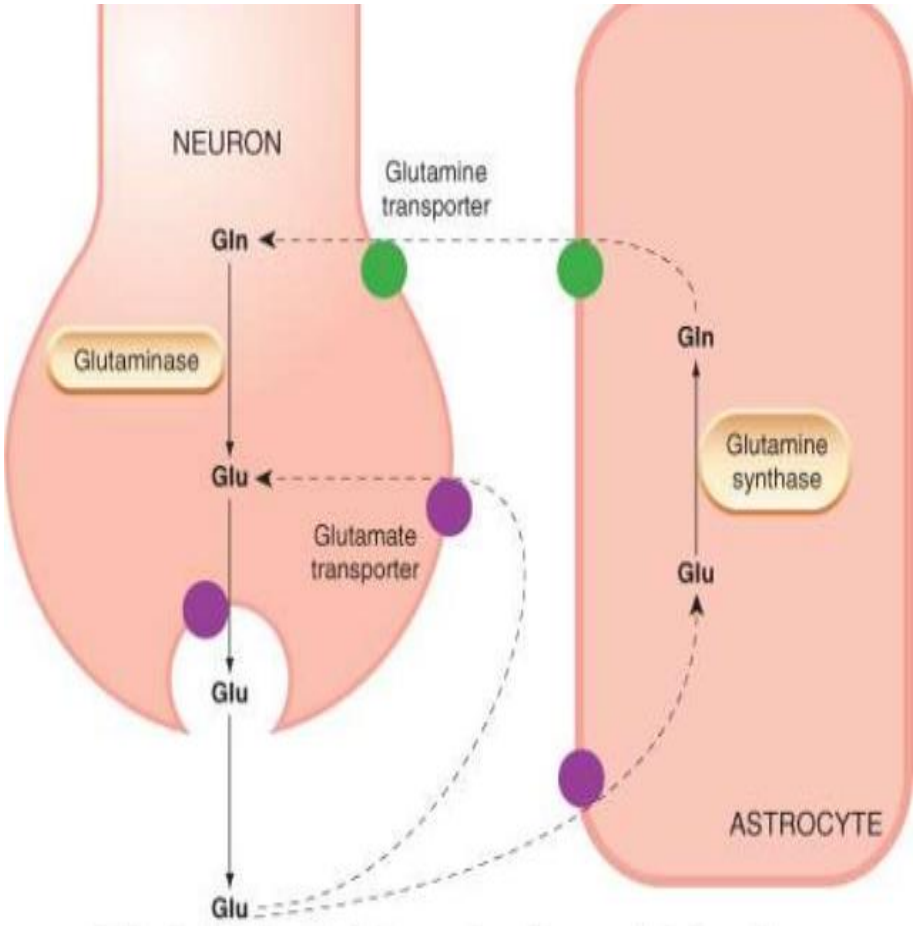
FUNCTIONS OF GLYCINE

- **Glycine** is precursor for a variety of important metabolites such as glutathione, porphyrins, purines, haem, and creatine.
- **Glycine** acts as neurotransmitter in central nervous system and it has many **roles** such as
  1)antioxidant
  2) anti-inflammatory,
  3)cryoprotective
  4)immunomodulatory in peripheral and nervous tissues.


WHAT IS GLUTAMATE?
An Examination of the Functions, Pathways and Excitation of the Glutamate Neurotransmitter

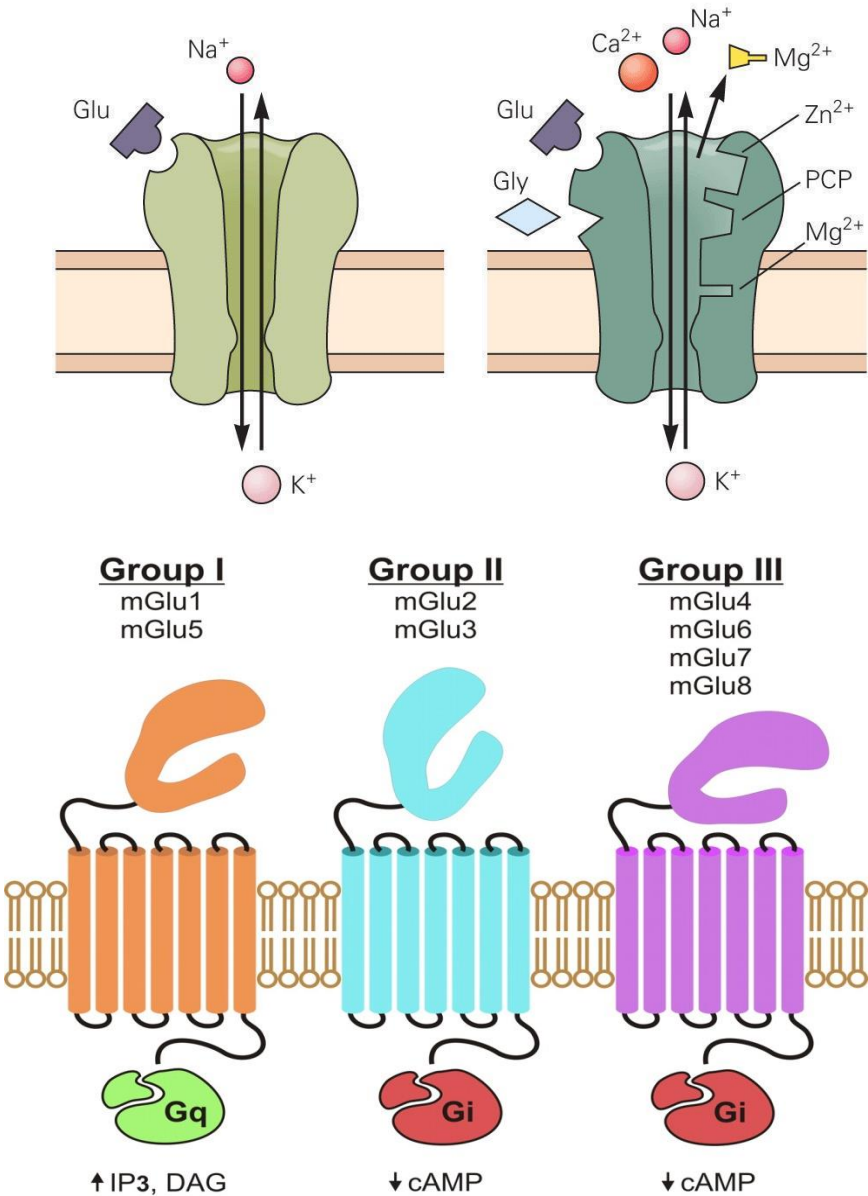
Synthesis , Storage & release

- **Synthesis**
- Glutamine comes to CNS through glial cells and kreb's cycle
- Converted to glutamate by glutaminase enzyme.
- **Stored** in vesicles
- **Released** by Ca^{2+} dependent exocytosis.



Glutamate receptors & functions

- Located on membranes of neuronal cells.
- Both iono tropic & meta botropic.
- Glutamate is most abundant & prominent excitatory neurotransmitter in the nervous system.
- Precursor for GABA, inhibitory neurotransmitter.



Functions of Glutamate

- Excitatory neurotransmitter in CNS, stored in neuronal cells.

Responsible for

- communication ,
- memory formation and
- learning .

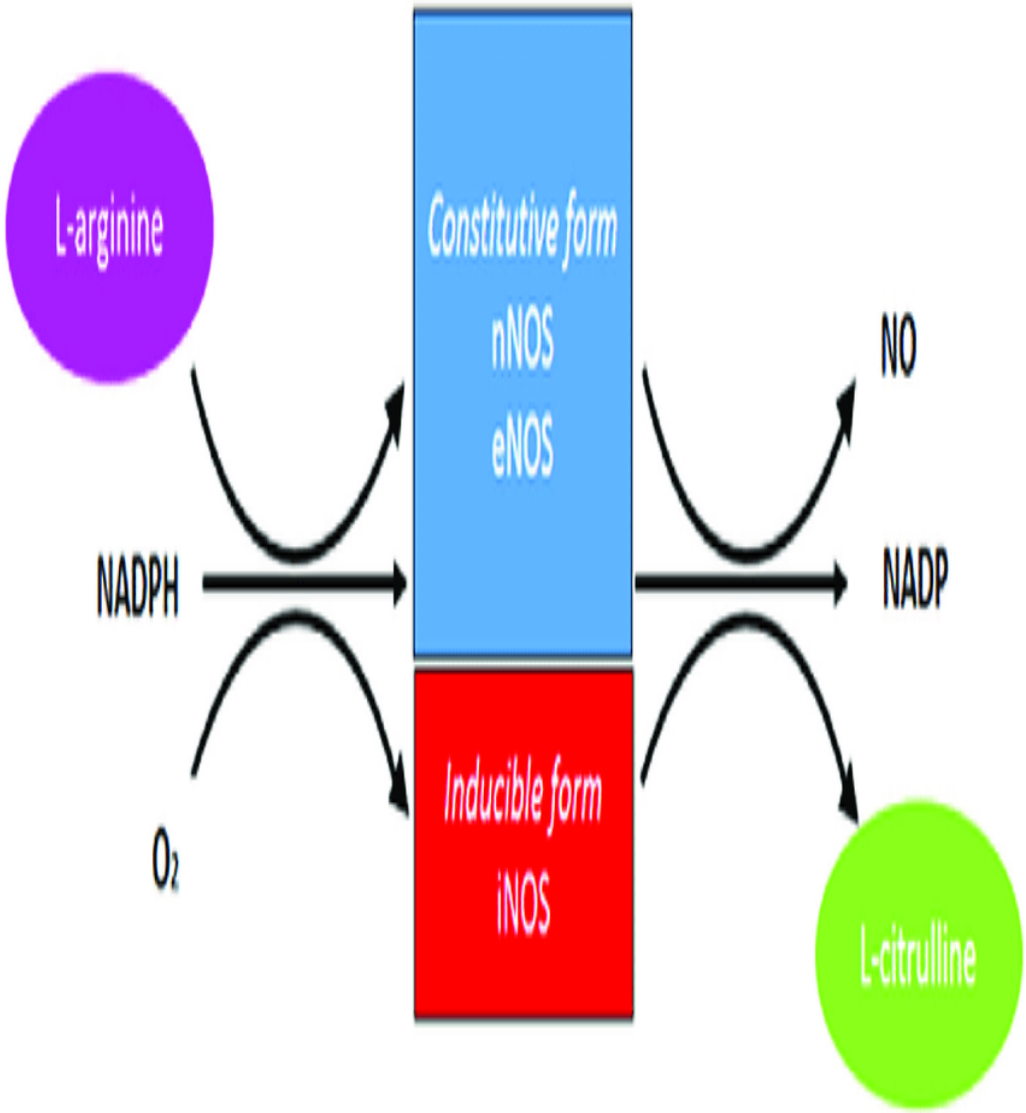
nitric oxide

Nitric oxide

- Simple ,unique, gaseous signaling molecule with free radicals properties
- Readily diffuses across the cell membrane
- Act as interacellular signaling molecule

Synthesis

- Synthesized from L-Arginine and molecular oxygen by enzyme nitric oxide synthase within synapse and used immediately.
- Three isoforms
- Endothelium(eNOS)
- Neurons(nNOS)
- Inducible(iNOS)



Storage

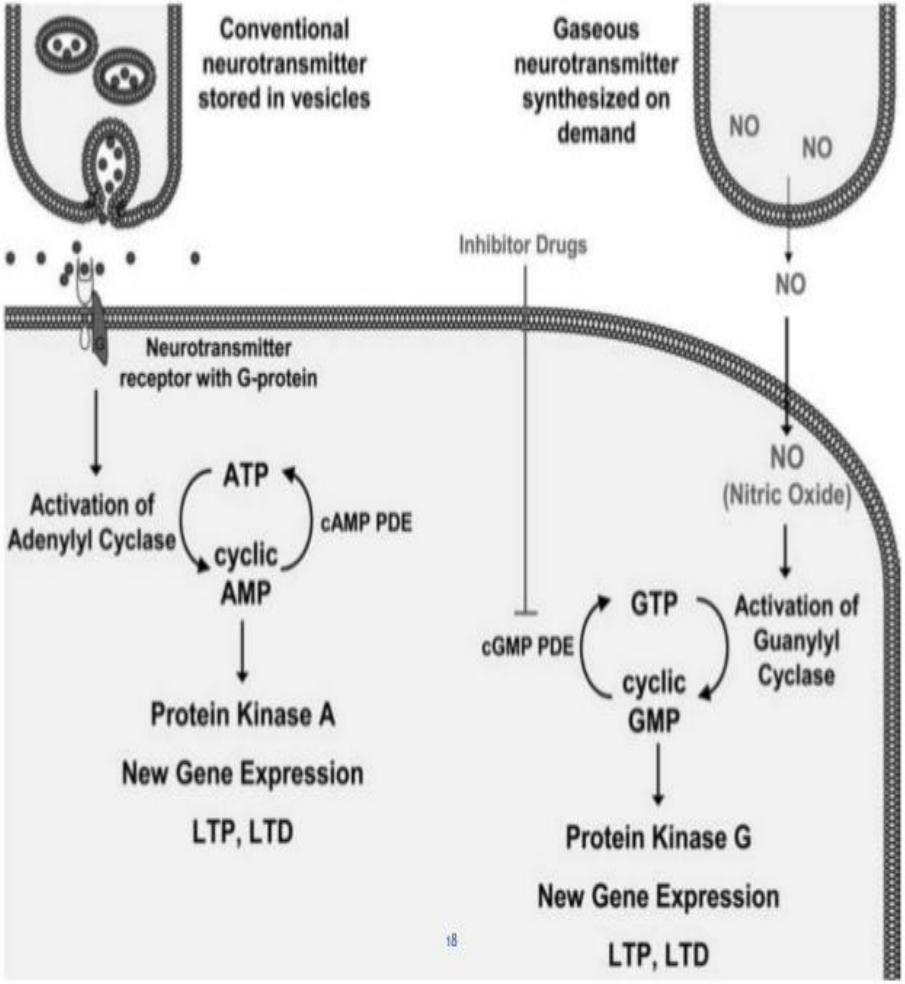
- **Nitric oxide does** not usually exist in its free form in the **body** due to its unstable nature but reacts with other molecules to form more stable products.
- In the blood, **nitric oxide** has a very short half-life and rapidly oxidises to nitrite.

Release

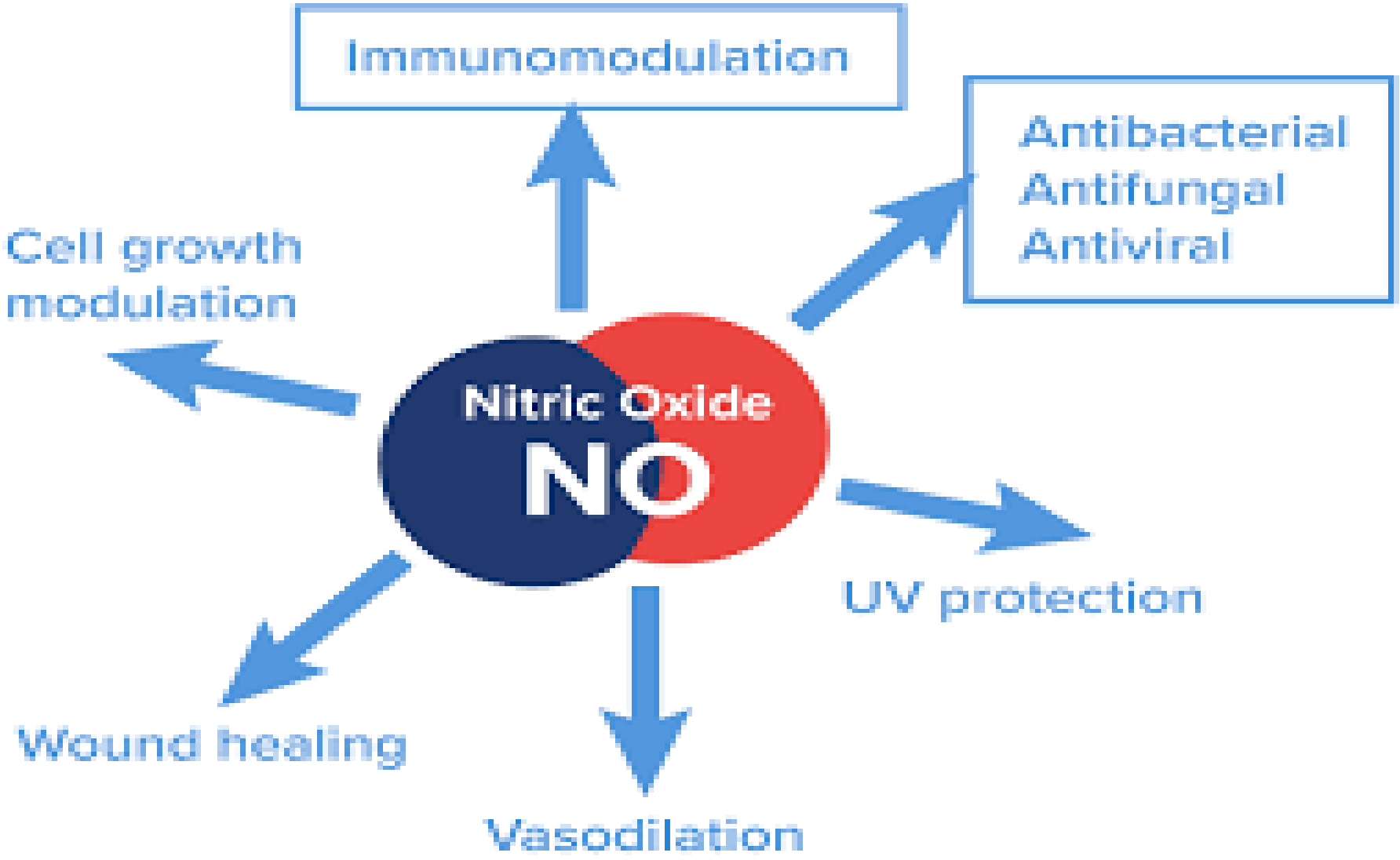
- A diet high in nitrate-rich vegetables and antioxidants or the use of supplements, such as L-arginine or L-citrulline, are beneficial ways to boost your body's natural production of **nitric oxide**.
- Other proven strategies include limiting mouthwash and exercising regularly.

Mechanism of action

- NO diffuses out of the cells making it, to post synaptic neurons.
- It does not bind to surface receptors, but instead binds with intracellular guanyl cyclase and activate cGMP production.
- This starts a cycle of nerve action potential.



Functions of nitric oxide



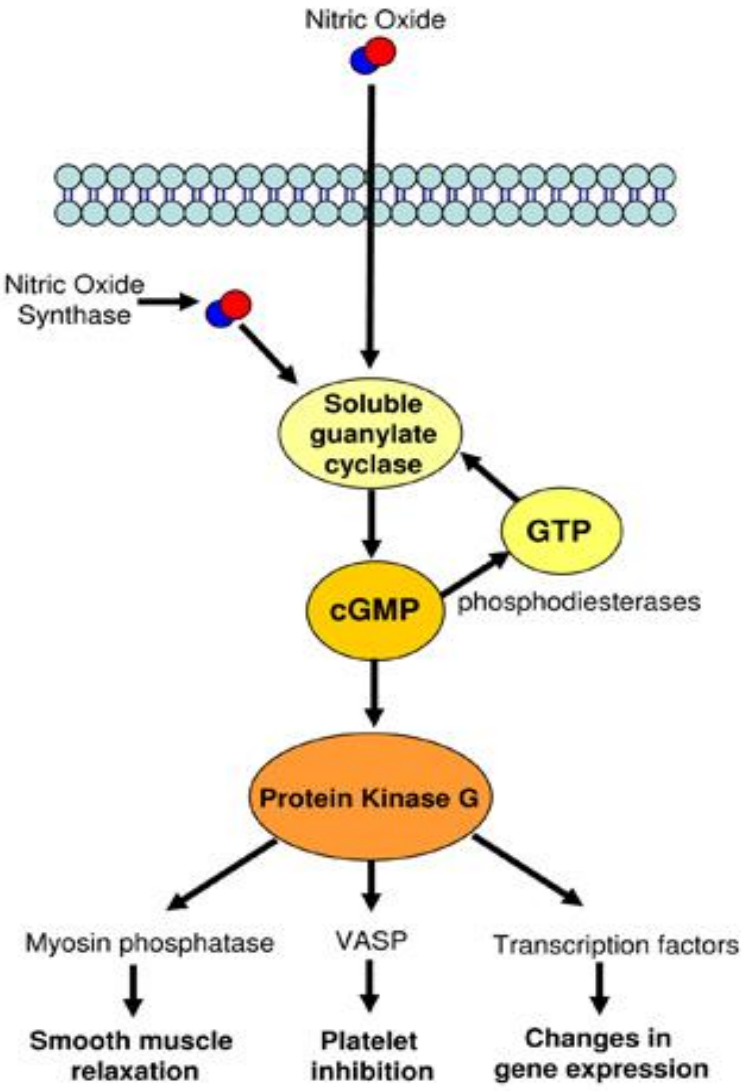
Functions

- Believed to play a role in long term memory.
- Its action in CNS is associated with pain perception in spinal cord.
- NO stimulates the secretion of many endocrine glands,e.g,

1)Gonadotropic releasing hormones

2)Release of pancreatic amylase

3)Release of adrenaline.




Q&A

Which one of the following neurotransmitters would you expect to find in the synapse during fast inhibitory synaptic transmission?

a. Acetylcholine
b. Dopamine
c. Glutamate
d. GABA
e. Noradrenalin

Which one of the following neurotransmitters would you expect to find in the synapse during fast inhibitory synaptic transmission?

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b. Dopamine
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d. GABA
e. Noradrenalin

- **The collective name for dopamine, serotonin and noradrenalin is:**

a. Amines
b. Anxiolytics
c. Hallucinogens
d. Neurotransmitters
e. Nuerotoxics

- **The collective name for dopamine, serotonin and noradrenalin is:**

a. Amines

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Thank
You